NANOMEDICINE CENTER CONCEPT DEVELOPMENT AWARDS

RELEASE DATE: May 4, 2004

RFA Number: RFA-RM-04-018

EXPIRATION DATE: July 27, 2004

Department of Health and Human Services (DHHS)

PARTICIPATING ORGANIZATION:
National Institutes of Health (NIH)
(http://www.nih.gov)

This RFA is developed as an NIH roadmap initiative (http://nihroadmap.nih.gov). All NIH Institutes and Centers participate in roadmap initiatives. The RFA will be administered by the National Eye Institute (NEI) on behalf of the NIH.

CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER(S): 93.867

APPLICATION RECEIPT DATE: July 26, 2004

THIS RFA CONTAINS THE FOLLOWING INFORMATION

PURPOSE OF THIS RFA

This RFA has two purposes:

o Part 1 – describes a new initiative to support a network of Nanomedicine Development Centers. This part of the RFA includes a description of an emerging NIH vision of Nanomedicine and the scientific basis driving this initiative.

o Part 2 – presents a solicitation of applications, or more aptly, "white papers," for applicants to request support for planning the Nanomedicine Development Centers.

o PART 1 – NANOMEDICINE INITIATIVE DESCRIPTION AND RESEARCH OBJECTIVES

Nanomedicine, an offshoot of nanotechnology, is a new term whose definition is evolving. In the present context, it refers to highly specific medical intervention at the molecular scale for curing disease or repairing tissue. To stimulate work in this field, the NIH will support a major research effort to obtain the fundamental knowledge required to make nanomedicine a reality. It is at this size scale – about 100 nm or less - that biological molecules form the basis of systems that provide structure, control, signaling, homeostasis, and motility in cells. There have been many scientific and technological advances in both the physical and biological sciences over the past several years that make nanomedicine research particularly attractive at this time. For example, new tools are being developed that permit imaging of structure at this scale, high speed measurement of the dynamic behavior of molecular assemblies, and measurement of forces at the molecular scale. These advances are complemented, on the biological side, by our knowledge of the human genome and a greater understanding of the molecular pathology of some diseases. The future of nanomedicine shows promise for providing us with better control of intracellular machinery, leading to better diagnostic tools and more specific treatments of disease with fewer side effects.

The NIH Nanomedicine Vision

A goal of this initiative is to characterize quantitatively the molecular scale components or nanomachinery of the cell and to precisely control and manipulate these molecules and supramolecular assemblies in living cells to improve human health. There are several other research efforts across the NIH in nanotechnology (http://www.becon.nih.gov/nano.htm). This Nanomedicine Initiative is distinguished from the others by its long-term focus on characterizing cellular processes and nanomachinery and their interactions at a level of precision that has not been achieved to date. This Initiative will exploit and build upon other research in nanotechnology, and apply it to studies of molecular systems in living cells which contain a multitude of nanoscale structures, such as membrane transporters; processes, such as self-assembly of protein-nucleic acid complexes; and nanomachines, such as molecular motors. Well controlled manipulation of these and other intracellular processes and structures has not

yet been achieved. As a first step, this initiative will define what is needed to precisely control cellular events at the molecular level including data collection, concept and model development, and creation of the physical tools for manipulating the processes and components in living cells. We anticipate that this knowledge will provide the essential scientific basis required to repair or replace damaged or diseased cellular systems.

Another important aspect of this initiative is the recognition that the precise control required to manipulate cellular components will require the understanding and use of engineering principles. To this end, the approach will be informed by the design principles gleaned from the molecular processes and structures found in living cells. In other words, biological tissues have evolved elegant, intricate pathways, molecular structures, and "devices" at the nanoscale. The long-term goal is to exploit these designs to build new nanoscale devices for biomedical use.

At present, there are gaps in our knowledge about most of the physical characteristics of cellular components such as their exact quantities and variations, location, timescales, interactions, affinities, force generation, flexibility and internal motion. Progress, using analytical models of molecular interactions already in hand, is stymied by this lack of information. More comprehensive models describing cellular structures and associations will be developed by using the knowledge gained from such precise quantitative physical measurements. To do so, new physical methods, instruments, and tools must be developed. In addition, computational tools for data collection, storage, analysis and dissemination must be refined.

In examining the long-term horizon, we expect that the next level of investigation will identify and define the design principles and operational parameters of naturally occurring nanostructures and complexes in cells. This knowledge will lead us to develop strategies and fabrication methods to build nanostructures, assemblies, and systems that ultimately will lead to specific control of various individual cellular components, from the smallest molecules to the largest organelles, in order to treat disease or repair damage.

If we are to achieve improved health by employing new nanoscale materials, then this initiative bears the responsibility to investigate interactions between the physical materials and devices that we develop and biological tissues. Most existing nanomaterials (e.g., carbon nanotubes and quantum dots) were not designed for biocompatibility or biodegradability. One of our goals is to design particles, materials, and devices that can be used in vivo.

What do we need to learn in order to engineer molecular-sized components? What types of measurements are lacking but, if made, could propel this effort forward? The following specific examples are presented only to illustrate what we mean by physical, quantitative measurements that may be required to fill gaps in our knowledge. We are not suggesting these as topics of particular interest to this initiative or as areas that are any more or less in need than others, but as examples to convey the ideas presented above.

Protein-Protein Interactions. Knowledge of protein interactions is crucial for understanding the pathways and networks operating within and between cells. Collection of protein-protein interaction information on a genome-wide basis is now possible. However, most of the approaches available today fall short of gathering the needed information. Yeast two-hybrid measurements, for example, remove the protein-coding DNA sequences from the cells of origin and place them in an artificial environment. In doing so, subtleties of the actual intracellular behavior are lost as a consequence of this experimental manipulation. The results are also not quantitative, for instance, with respect to binding constants. The next generation of tools will need to enable both qualitative and quantitative studies on the precise protein interactions in situ.

Intracellular Transport. The transport systems present in eukaryotic cells organize and move organelles within the cytoplasm, orchestrate and implement the distribution of replicated chromosomes to daughter cells, and are the basic machinery of cellular migration. Years of innovative research have generated detailed knowledge of the cellular organization and control of these dynamic systems. Mathematical models of their operation have been developed, but many key parameters, such as, rates of polymerization, nucleation, capping, or dissociation, must be estimated because they cannot be measured directly. Indeed, measurements central to the functions of these transport systems, such as stresses on the fibers, forces generated by assembly of the fibers or by interactions of fibers with the motors or other cellular structures, and force and dynamics of adhesion to substrates currently cannot be measured in vivo.

Biomolecular Dynamics. Often, measurements of molecular processes on a biologically relevant timescale are inadequate. For example, studies of second messenger signaling require harvesting tens of thousands of cells to measure significant changes of intracellular concentrations of relevant molecules. The methods require substantial time, at least on the order of seconds, before the first data points are measured. Is 10 seconds a rapid enough measurement? 5 seconds? Are studies with techniques that require such large quantities of material feasible or necessary for precision studies of nanoscale events? Is the information from these types of studies adequate to lead to the precision required for more refined, quantitative models? Clearly, a very different set of tools is needed to probe intracellular molecular events on the biologically-relevant timescales of milliseconds or even microseconds.

These are just a few examples that typify the shortcomings in available knowledge and technology. A primary goal of the Nanomedicine Initiative is to stimulate development of radically new technologies that might provide novel strategies and new insights for cell biological studies of intracellular molecular interactions.

Formulating the Program for a Network of Nanomedicine Development Centers

Based on discussions with hundreds of scientists early in the planning for the NIH Roadmap (Zerhouni, E., 2003, Science 302:63-72), the following concepts have been developed for the Nanomedicine Development Centers program. While it is anticipated that the final program will have many of the features outlined here, the NIH invites the

research community, through the processes initiated in this RFA, to help to formulate this program.

Initially, work at the Centers will determine what additional measurements and analytical and computational tools are needed to understand biological system design at the molecular level. Next, the Centers will develop, refine, and apply them to biological systems. This, in turn, will lead to using the knowledge to engineer molecular structures, assemblies, and organelles for treating diseased or damaged cells and tissues. We anticipate that reaching all of these goals may require ten years or more.

Each of the Nanomedicine Development Centers will be formed around a specific theme that will serve as a model on which to focus studies of broader relevance. For example, a Center may choose a model molecular system or pathway, such as a particular signaling pathway, a system of molecular motors, a proteasomal degradation pathway, an energy transduction system, or the transport of materials across membranes. Alternatively, a Center may choose a cell type or disease as a model. Regardless of the specific theme, the focus will be on the biological system and its relevance to health, not on the technological approach, per se, since several technologies will most likely be required to acquire the range of physical data types needed to solve the biomedical problem. Nonetheless, the expectation is that the level of technology development in the Centers will be high.

Additionally, each center will develop new tools as well as refine existing ones, evaluate materials on which the tools will be based, generate tools that can be used at large scale and high throughput, and develop novel algorithms and modular systems for analysis and data handling that can be merged with tools developed by other groups.

Another emphasis of this program is to develop new tools and knowledge that can be generalized and therefore transcend any individual model pathway, molecular assembly, cell type, or disease. Although work may begin with well characterized models, greater efforts should be devoted to developing tools whose potential for application is broader than the individual model system or class of problem (e.g., cytoskeleton vs. signaling pathway vs. ion channels vs. machinery for replication, transcription or translation). Optimal measurement tools would be sufficiently powerful and generic that they would not need to be re-created for each molecule (e.g., today we must produce a GFP reporter construct for every gene and gene variant we wish to study, or several constructs to conduct FRET studies of molecular rearrangements). Given this approach, it will be essential for the Nanomedicine Centers to collaborate on setting priorities and resource allocation with other Nanomedicine Centers, in order to maximize the resources and capabilities of the Centers. That is, each Center would not be expected to be comprehensive but would operate as part of a network so that new capabilities are generated efficiently and without redundancy.

These Centers will require collaboration by scientists from disciplines that may not typically interact with each other. For example, Centers might be populated with cell biologists, mathematicians, biochemists, engineers, molecular biologists, statisticians, etc.

A key to progress in nanomedicine is the development of multi- and interdisciplinary teams of scientists who together will define the properties, knowledge, and concepts required by this initiative.

Implementing this Initiative for Developing a Network of Nanomedicine Centers

This Centers program will be developed and implemented in a different fashion from standard NIH procedures. The scientific scope and the administrative structure required for the Nanomedicine Development Centers are currently only partially defined. The NIH Nanomedicine Roadmap Implementation team has devised a novel plan to work with the scientific community to develop the scientific and organizational ideas that will lead to a solicitation for applications to generate these centers. Our plan will be distinguished by a high level of interaction of potential applicants with each other and with NIH staff prior to announcing the final solicitation. This process was designed to stimulate new collaborations that will result in more effective Centers. We expect that this high degree of interaction will lead to Centers that operate as a network, with each Center working on a unique set of problems but cooperating and sharing information with the others. Once the Centers are funded, the NIH will continue to facilitate interaction and collaboration among Centers with periodic meetings of key Center scientific representatives.

A three-step process for applicants has been developed. APPLICANTS MUST PARTICIPATE IN EACH STEP OF THE PROCESS TO BE ELIGIBLE TO APPLY FOR THE CENTER GRANT IN 2005.

Step 1: Concept Development Memo (CDM) - the short “white paper”

The CDM will broadly outline the applicant's vision for the content and structure for a nanomedicine center, as well as how planning funds would be used to further develop this vision. Successful applicants will receive a Concept Development Award (CDA) for developing a more extensive plan for a Nanomedicine Center. The specific requirements for preparing the “white paper” are outlined in PART 2 of this RFA (see below).

Step 2: Concept Development Plans (CDP) – the long “white paper”

The product of the Concept Development Award is the CDP. The best features from the submitted CDPs will be incorporated into the final solicitation for the Nanomedicine Development Centers.

Step 3: Nanomedicine Development Center Application

Only applicant teams who have submitted both the CDM and CDP will be eligible to apply for funding for a Nanomedicine Development Center in 2005.

The NIH Roadmap has set aside $6 million annually for Nanomedicine Development Centers beginning in 2005. It is anticipated that three or four awards for up to five years, will be made. Pending availability of additional funds in 2006, the initial Centers may be

expanded, or additional awards will be made, or both. If additional awards are to be made, this second solicitation would be open to the entire research community.

o PART 2 – SOLICITATION OF THE CONCEPT DEVELOPMENT MEMO (CDM)

The CDM is a brief "white paper" that outlines the applicant's vision for a Nanomedicine Development Center and the set of problems the center might try to solve. This vision should begin with the concepts described in this RFA, and develop them further based upon the applicant's understanding of the science, the technology, and the medical needs. The applicant should also propose a structure for the proposed center and include a budget and justification to support activities necessary to prepare a Concept Development Plan (CDP, see below). Concept Development Awards (CDA) will be made by September 30, 2004, and the deadline for CDPs will be February 15, 2005. Therefore, in their CDM, applicants should propose a budget that can be used effectively during this time period to gather key investigators for planning meetings, to organize small workshops with members of other scientific, clinical or engineering communities, or organize any other planning activities that will facilitate the assembly of teams and the production of a CDP. The award notice for the CDA will contain an explicit term, requiring submission of a CDP to the NIH by February 15, 2005.

Applicants submitting a CDM for obtaining a Concept Development Award need to understand the next steps in this process, because the CDM and CDA lead directly to submission of the Concept Development Plan (CDP). Therefore, even though this RFA only solicits the CDM, information about the CDP and subsequent steps is presented here.

The Concept Development Plan (CDP) will be a more extensive, substantive, "white paper" to (1) describe a vision for the proposed NIH Nanomedicine Development Center, (2) describe the specific scientific and technical approaches that the applicant team would propose in the subsequent Center application, and (3) propose a structure for the overall NIH Nanomedicine program, including how each Center, and the network of Centers, should be structured and should operate. The notion that these Centers will operate as a network is driven not only by the high value of collaborative interactions but also by the benefits derived from sharing essential, expensive resources, and avoiding duplication of efforts.

The vision for this Nanomedicine Initiative, expressed in this RFA, is intentionally ambitious. Because this vision may evolve, the scientific goals and structural ideas of how these Centers will operate may also change. Thus, the CDP components requested in the previous paragraph should be written to explicitly address this ambitious vision but in a critical, rigorous fashion that might also include refining the vision and ideas expressed here.

The CDP will include a 2 to 3 page public abstract that will be shared with all participants in a meeting to be held at the NIH in approximately March 2005, to which all authors of substantive CDPs will be invited. The CDP will also include 15-20 pages that

will be held in confidence and used, by NIH staff and a group of scientific consultants, in combination with information exchanged at the March 2005 meeting, as a basis for the formal solicitation for the Nanomedicine Development Centers. Further instructions for preparing the CDP will be provided to CDA awardees.

In summary, the timetable for awarding the first group of Nanomedicine Development Centers is as follows:

May 4, 2004 Public meeting to describe this RFA and the overall Nanomedicine Initiative

July 26, 2004 Receipt of Concept Development Memos (step 1)

September 30, 2004 Funding of Concept Development Awards

February 15, 2005 Receipt of Concept Development Plans (step 2)

March 2005 Meeting of submitters of Concept Development Plans

April 2005 Publication of solicitation for Nanomedicine Development Centers

July 12, 2005 Receipt of applications for Nanomedicine Development Centers (step 3)

September 2005 Funding of Nanomedicine Development Centers

MECHANISM OF SUPPORT

This RFA will use a Flexible Research Authority PN1, Nanomedicine Concept Development Award mechanism. As an applicant you will be solely responsible for planning, directing, and executing the proposed project. This RFA is a one-time solicitation. The anticipated award date is September 30, 2004.

FUNDS AVAILABLE

The NIH intends to commit approximately $1.5 million in FY 2004 to fund approximately 20 new awards in response to this RFA. An applicant may request a project period of up to 6 months and a budget for direct costs of up to $50,000 (plus associated F&A). Although the financial plans of the NIH provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications (CDMs). This initiative may be repeated in future years depending on the success of the program and the availability of funds.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

o For-profit or non-profit organizations
o Public or private institutions, such as universities, colleges, hospitals, and laboratories
o Units of State and local governments
o Eligible agencies of the Federal government
o Foreign institutions are not eligible to apply, but may collaborate with U.S. institutions and may receive funding.

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application (CDM) for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

SPECIAL REQUIREMENTS

The CDM is the first of three steps for applicants. In order to be eligible to submit an application for a Nanomedicine Development Center in July 2005, applicants must have submitted a Concept Development Memo, must have received a Concept Development Award, and must have submitted a Concept Development Plan.

The principal investigator or any other co-investigators listed in the CDM may be the lead author of the CDP, and the lead author or any co-investigator listed in the CDP may be designated as the principal investigator of the Center application. Thus, the PI and/or applicant institution may change but must meet all eligibility requirements. However, we expect that each CDA can lead to only one CDP, and each CDP can only lead to one Nanomedicine Center application.

Submission of a Concept Development Plan (CDP) by February 15, 2005, will be an explicit requirement of the Notice of Award for all Concept Development Awards.

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into two areas: scientific/research/peer review or financial/grants management issues:

o Direct your questions about scientific/research/review issues to:

Richard S. Fisher, Ph.D.
Division of Extramural Research
National Eye Institute
5635 Fishers Lane, Room 1300
Bethesda, MD 20892-9300
Telephone: (301) 451-2020
Email: fisherR@mail.nih.gov

o Direct your questions about financial/grants management matters to:

Mr. William Darby
Chief, Grants Management Branch
Division of Extramural Research
National Eye Institute
5635 Fishers Lane, Room 1300
Bethesda, MD 20892-9300
Telephone: (301) 451-2020
Email: darby2@mail.nih.gov

SUBMITTING AN APPLICATION

Applications (CDMs) must be prepared using only the specified pages from PHS 398 research grant application instructions and forms (rev. 5/2001; see below, SUPPLEMENTARY INSTRUCTIONS). Applications must have a Dun and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at http://www.dunandbradstreet.com/. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 document is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

SUPPLEMENTARY INSTRUCTIONS

The Concept Development Memo (CDM) consists of two sections:

o Use only the following PHS 398 pages: Face Page (Form Page 1); Description, Performance Sites, and Key Personnel page (Form Page 2); Detailed Budget for Initial Budget Period (Form Page 4) including justification; Biographical Sketches for the P.I. and Key Personnel; and Checklist Form Page (include as the last page of the application).

o A white paper, in PHS 398 Continuation Page format using standard font, spacing and margin rules. The white paper should be structured as the applicant finds most effective. The white paper may not exceed five pages and must be self-contained including any

figures. No appendix material or website links for additional information are acceptable. The CDM must include:

- a broad outline of the applicant's vision for a Nanomedicine Development Center, with emphasis on the set of problems the center might try to solve, and a preview of the approaches that might be used. This vision should explicitly address the concepts described in this RFA and should develop them further based upon the applicant's understanding of the scientific, technological and medical needs. Applicants are encouraged to think more broadly than their current research program and begin developing collaborations that would be further cultivated if the CDM results in an award (CDA). The characteristics of the proposed team, such as expertise and other required broad capabilities, should be described even if all of the key individuals have not yet been identified. It would be advantageous if some of the potential collaborators contribute to the development of the CDM.

- a plan for using the Concept Development Award to produce the Concept Development Plan (described above) including a justified budget. The budget may include funds for travel, workshops, and other activities required to facilitate planning for submission of a Concept Development Plan. Up to $1000 each for the P.I. and up to two co-investigators, to participate in the March 2005 meeting at NIH, may also be included.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/labels.pdf.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application (CDM), including the Checklist, and three signed, photocopies, in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

At the time of submission, two additional copies of the application must be sent to:
Richard S. Fisher, Ph.D.
Division of Extramural Research
National Eye Institute
5635 Fishers Lane, Room 1300
Bethesda, MD 20892-9300
Email: fisherR@mail.nih.gov

APPLICATION PROCESSING: Applications must be received on or before the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness and responsiveness by NIH staff. Incomplete applications will not be reviewed. If the application is not responsive to the RFA, it will be returned to the applicant without review.

Applications that are complete and responsive to the RFA will be evaluated by a Nanomedicine Evaluation Panel comprised of the Nanomedicine Roadmap Implementation Working Group members and outside scientific review consultants.

Applications will be reviewed and ranked in accordance with the review criteria stated below. Applicants will receive a brief written summary of the outcome of the review.

REVIEW CRITERIA

The following topics will be evaluated in the merit review of the CDM. The Panel will weight the topics as appropriate for each application.

1. Merit of proposal for the applicant's vision of a Nanomedicine Development Center. The relevance of the proposed Center to the Nanomedicine Roadmap Initiative will be evaluated. The evaluation of the proposal may include but is not limited to:

- Justification for the model system(s) chosen
- Toolbox to be applied and developed
- Clarity of analysis of the shortcomings of current capabilities and impediments to be overcome
- Approach to generalizing results/solutions
- Anticipated design principles to be learned from the model system
- Analysis of the need for collaborative areas and interdisciplinary interactions
- Approach to efficiently integrating with ongoing efforts and existing/emerging resources
- Qualifications of the investigative team

2. Merit of validity and creativity for using requested planning funds to facilitate the planning and writing of the Concept Development Plan (CDP).

The appropriateness of the proposed budget for planning activities will also be evaluated but will not be incorporated into the CDM ranking.

RECEIPT AND REVIEW SCHEDULE

Application Receipt Date: July 26, 2004
Scientific Merit Review Date: August 2004
Earliest Anticipated Start Date: September 30, 2004
Receipt of CDP: February 15, 2005

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

- Scientific merit (as determined by review)
- Availability of funds
- Programmatic priorities.

REQUIRED FEDERAL CITATIONS

AUTHORITY AND REGULATIONS: AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284), FY 2004 Consolidated Appropriations Resolution P.L. 108-199, Sections 221, (a) and (b). All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Return to Volume Index

Return to NIH Guide Main Index
